

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/135	A1	(11) International Publication Number: WO 99/15163 (43) International Publication Date: 1 April 1999 (01.04.99)
<p>(21) International Application Number: PCT/US98/18103</p> <p>(22) International Filing Date: 1 September 1998 (01.09.98)</p> <p>(30) Priority Data: 60/059,628 23 September 1997 (23.09.97) US</p> <p>(71) Applicant (for all designated States except US): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).</p> <p>(72) Inventor; and (73) Inventor/Applicant (for US only): HEILIGENSTEIN, John, Harrison [US/US]; 1202 West 56th Street, Indianapolis, IN 46228 (US).</p> <p>(74) Agents: TITUS, Robert, D. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).</p>		<p>(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>
<p>(54) Title: TREATMENT OF CONDUCT DISORDER</p> <p>(57) Abstract</p> <p>Norepinephrine reuptake inhibitors are used to treat conduct disorder.</p> <p>BEST AVAILABLE COPY</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon		Republic of Korea	PT	Portugal		
CN	China	KR	Republic of Korea	RO	Romania		
CU	Cuba	KZ	Kazakhstan	RU	Russian Federation		
CZ	Czech Republic	LC	Saint Lucia	SD	Sudan		
DE	Germany	LI	Liechtenstein	SE	Sweden		
DK	Denmark	LK	Sri Lanka	SG	Singapore		
EE	Estonia	LR	Liberia				

TREATMENT OF CONDUCT DISORDER

The invention belongs to the fields of pharmaceutical chemistry and psychiatric medicine, and provides a method of treatment of the psychiatric disorder known as conduct disorder.

A significant number of children and adolescents display a behavioral disorder which suggests total disregard for the basic rights of others, far exceeding the expected idiosyncrasies of the developing individual. Children and adolescents with these conduct disorders have considerable difficulty behaving in a socially acceptable way and in following rules at school and at home. The conduct disorder patient typically exhibits aggressive behavior toward people and animals, is deceitful, lies, steals, destroys the property of others, is truant from school, runs away from home, as well as a variety of additional antisocial symptoms. When untreated, children and adolescents suffering with conduct disorders are typically very unhappy and face a difficult future. They are unable to cope with the demands of adulthood, have continuing problems maintaining relationships, are unable to hold a job, and often break the law and behave antisocially.

Current therapies for the treatment of conduct disorders are not totally satisfactory. Methylphenidate (Ritalin™), which exhibits noradrenergic and dopaminergic effects, has been reported to induce improvement in many patients' symptoms (Shah, et al., *Journal of Child and Adolescent Psychopharmacology*, 4(4), 255-261 (1994)). Some patients, however, were refractory to methylphenidate dosing, and others were unable to be maintained on the treatment for long periods of time. Furthermore, due to the high potential for substance abuse in conduct disorder patients, the use of stimulants such as methylphenidate is

problematic. Shah also demonstrated that certain patients benefited from the augmentation of methylphenidate treatment by the addition of pemoline, a dopamine reuptake inhibitor. Haloperidol and lithium carbonate have found utility in the treatment of the aggressive symptoms of conduct disorder (Platt, et al., *Arch. Gen. Psychiatry*, 41, 657-662 (1984)), but both are associated with undesirable side effects, including negative effects on cognition.

The need for a safe and effective treatment for conduct disorders, without the disadvantages of current therapies, continues to be a concern of the psychiatric community.

The present invention provides a method of treating conduct disorder comprising the administration to a patient in need of such treatment of an effective amount of a norepinephrine reuptake inhibitor.

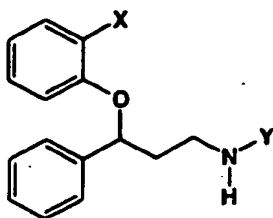
Many compounds, including those discussed at length below, are norepinephrine reuptake inhibitors, and no doubt many more will be identified in the future. In the practice of the present invention, it is intended to include reuptake inhibitors which show 50% effective concentrations of about 1000 nM or less, in the protocol described by Wong et al., *Drug Development Research*, 6, 397 (1985). The norepinephrine reuptake inhibitors useful for the method of the present invention are characterized in being selective for the inhibition of neurotransmitter reuptake relative to their ability to act as direct agonists or antagonists at other receptors. Norepinephrine reuptake inhibitors useful for the method of the present invention include, but are not limited to:

Tomoxetine, (R)-(-)-N-methyl-3-(2-methylphenoxy)-3-phenylpropylamine, is usually administered as the hydrochloride salt. Tomoxetine was first disclosed in U.S. Patent #4,314,081. The word "tomoxetine" will be used here

-3-

to refer to any acid addition salt or the free base of the molecule. See, for example, Gehlert, et al., *Neuroscience Letters*, 157, 203-206 (1993), for a discussion of tomoxetine's activity as a norepinephrine reuptake inhibitor;

The compounds of formula I:



I

wherein X is C₁-C₄ alkylthio, and Y is C₁-C₄ alkyl or a pharmaceutically acceptable salt thereof. The compounds of formula I were described in U.S. Patent 5,281,624, of Gehlert, Robertson, and Wong, and in Gehlert, et al., *Life Sciences*, 55(22), 1915-1920, (1995). The compounds are there taught to be inhibitors of norepinephrine reuptake in the brain. It is also explained that the compounds exist as stereoisomers, and that they accordingly include not only the racemates, but also the isolated individual isomers as well as mixtures of the individual isomers. For example, the compounds of formula I include the following exemplary species:

N-ethyl-3-phenyl-3-(2-methylthiophenoxy)propylamine benzoate;

(R)-N-methyl-3-phenyl-3-(2-propylthiophenoxy)propylamine hydrochloride;

(S)-N-ethyl-3-phenyl-3-(2-butylthiophenoxy)propylamine;

N-methyl-3-phenyl-3-(2-ethylthiophenoxy)propylamine malonate;

(S)-N-methyl-3-phenyl-3-(2-tert-butylthiophenoxy)-propylamine naphthalene-2-sulfonate;

(R)-N-methyl-3-(2-methylthiophenoxy)-3-phenyl-propylamine;

5 Reboxetine (Edronax™), 2-[α -(2-ethoxy)phenoxy-benzyl]morpholine, is usually administered as the racemate. It was first taught by U.S. Patent 4,229,449, which describes its utility for the treatment of depression. Reboxetine is a selective norepinephrine reuptake inhibitor.
10 The term "reboxetine" will be used here to refer to any acid addition salt or the free base of the molecule existing as the racemate or either enantiomer;

 Duloxetine, N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine, is usually administered as the
15 hydrochloride salt and as the (+) enantiomer. It was first taught by U.S. Patent 4,956,388, which shows its high potency. The word "duloxetine" will be used here to refer to any acid addition salt or the free base of the molecule;

 Venlafaxine is known in the literature, and its
20 method of synthesis and its activity as an inhibitor of serotonin and norepinephrine uptake are taught by U.S. Patent 4,761,501. Venlafaxine is identified as compound A in that patent; and

 Milnacipran (N,N-diethyl-2-aminomethyl-1-
25 phenylcyclopropanecarboxamide) is taught by U.S. Patent 4,478,836, which prepared milnacipran as its Example 4. The patent describes its compounds as antidepressants. Moret et al., *Neuropharmacology* 24, 1211-19 (1985), describe its pharmacological activities as an inhibitor of serotonin and
30 norepinephrine reuptake.

 All of the U.S. patents which have been mentioned above in connection with compounds used in the present invention are incorporated herein by reference.

A preferred duloxetine enteric formulation is a pellet formulation comprising a) a core consisting of duloxetine and a pharmaceutically acceptable excipient; b) an optional separating layer; c) an enteric layer comprising hydroxypropylmethylcellulose acetate succinate (HPMCAS) and a pharmaceutically acceptable excipient; d) an optional finishing layer. The following example demonstrates the preparation of a preferred such formulation.

Example

10 mg Duloxetine base/capsule

Bill of Materials

Beads

Sucrose - starch nonpareils,

15	20-25 mesh	60.28 mg
----	------------	----------

Duloxetine layer

Duloxetine	11.21
------------	-------

Hydroxypropylmethylcellulose	3.74
------------------------------	------

Separating layer

20	Hydroxypropylmethylcellulose	2.51
----	------------------------------	------

Sucrose	5.00
---------	------

Talc, 500 mesh	10.03
----------------	-------

Enteric layer

HPMCAS, LF grade, Shin-Etsu Chemical 25.05

25 Co., Tokyo, Japan

Triethyl citrate	5.00
------------------	------

Talc, 500 mesh	7.52
----------------	------

Finishing layer

Hydroxypropylmethylcellulose 8.44

30	Titanium dioxide	2.81
----	------------------	------

Talc Trace

141.60 mg

-6-

The duloxetine layer was built up by suspending duloxetine in a 4% w/w solution of the hydroxypropylmethyl-cellulose in water, and milling the suspension with a CoBall Mill (Fryma Mashinen AG, Rheinfelden, Switzerland) model MS-12. A fluid bed dryer with a Wurster column was used to make this product, at a batch size of 1.0 kg. The separating layer was added from a 4% w/w solution of the hydroxypropyl-methylcellulose in water, in which the sucrose was also dissolved:

In order to prepare the enteric coating suspension, purified water was cooled to 10°C and the polysorbate, triethyl citrate and silicone emulsion were added and dispersed or dissolved. Then the HPMCAS and talc were added and agitated until homogeneity was obtained, and the HPMCAS was fully neutralized by addition of ammonium hydroxide until solution of the polymer was complete. To this suspension, a carboxymethylcellulose aqueous solution, 0.5% w/w, was added and blended thoroughly. The enteric suspension was maintained at 20°C during the coating process. The enteric suspension was then added to the partially completed pellets in the Wurster column at a spray rate of about 15 ml/min, holding the temperature of the inlet air at about 50°C. The product was dried in the Wurster at 50°C when the enteric suspension had been fully added, and then dried on trays for 3 hours in a dry house at 60°C. A finishing layer was then applied which consisted of a 4.5% w/w/ hydroxypropylmethyl-cellulose solution containing titanium dioxide and propylene glycol as plasticizer. The pellets were completely dried in the fluid bed dryer and then were then filled in size 3 gelatin capsules.

While all compounds exhibiting norepinephrine reuptake inhibition are useful for the method of the present invention, certain are preferred. It is preferred that the

-7-

norepinephrine reuptake inhibitor is selective for norepinephrine over other neurotransmitters. It is also preferred that the norepinephrine reuptake inhibitor is selected from tomoxetine, reboxetine, or a compound of formula I. It is especially preferred that the norepinephrine reuptake inhibitor be selected from tomoxetine, reboxetine, or (R)-N-methyl-3-(2-methylthiophenoxy)-3-phenylpropylamine.

It will be understood by the skilled reader that most or all of the compounds used in the present invention are capable of forming salts, and that the salt forms of pharmaceuticals are commonly used, often because they are more readily crystallized and purified than are the free bases. In all cases, the use of the pharmaceuticals described above as salts is contemplated in the description herein, and often is preferred, and the pharmaceutically acceptable salts of all of the compounds are included in the names of them.

Many of the compounds used in this invention are amines, and accordingly react with any of a number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Since some of the free amines of the compounds of this invention are typically oils at room temperature, it is preferable to convert the free amines to their pharmaceutically acceptable acid addition salts for ease of handling and administration, since the latter are routinely solid at room temperature. Acids commonly employed to form such salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids, such as *p*-toluenesulfonic acid, methanesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid and the like. Examples of such

pharmaceutically acceptable salts thus are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, b-hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable salts are those formed with hydrochloric acid.

Administration

The dosages of the drugs used in the present invention must, in the final analysis, be set by the physician in charge of the case, using knowledge of the drugs, the properties of the drugs in combination as determined in clinical trials, and the characteristics of the patient, including diseases other than that for which the physician is treating the patient. General outlines of the dosages, and some preferred dosages, can and will be provided here.

Tomoxetine: from about 5 mg/day to about 100 mg/day; preferably in the range from about 5 to about 70 mg/day; more preferably from about 10 to about 60 mg/day; and still more preferably from about 10 to about 50 mg/day;

Compounds of formula I: from about 0.01 mg/kg to about 20 mg/kg; preferred daily doses will be from about

-9-

0.05 mg/kg to 10 mg/kg; ideally from about 0.1 mg/kg to about 5 mg/kg;

Reboxetine: from about 1 to about 30 mg, once to four times/day; preferred, from about 5 to about 30 mg once/day;

Duloxetine: from about 1 to about 30 mg once/day; preferred, from about 5 to about 20 mg once/day;

Venlafaxine: from about 10 to about 150 mg once-thrice/day; preferred, from about 25 to about 125 mg thrice/day; and

Milnacipran: from about 10 to about 100 mg once-twice/day; preferred, from about 25 to about 50 mg twice/day.

All of the compounds concerned are orally available and are normally administered orally, and so oral administration is preferred. However, oral administration is not the only route or even the only preferred route. For example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine. The drugs may also be administered by the percutaneous, intravenous, intramuscular, intranasal or intrarectal route, in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs and the convenience of the patient and the caregiver.

The best description of conduct disorder is the diagnostic criteria published by the American Psychiatric Association in the DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised (1987)), as follows.

Diagnostic criteria for Conduct Disorder

A. A disturbance of conduct lasting at least six months, during which at least three of the following have been present:

- 5 (1) has stolen without confrontation of a
victim on more than one occasion
(including forgery)
- (2) has run away from home at least twice
while living in parental or parental
surrogate home (or once without
returning)
- 10 (3) often lies (other than to avoid physical
or sexual abuse)
- (4) has deliberately engaged in fire-setting
- (5) is often truant from school (for older
person, absent from work)
- (6) has broken into someone else's house,
building, or car
- 15 (7) has deliberately destroyed others'
property (other than fire-setting)
- (8) has been physically cruel to animals
- (9) has forced someone into sexual activity
with him or her
- 20 (10) has used a weapon in more than one fight
- (11) often initiates physical fights
- (12) has stolen with confrontation of a
victim (e.g., mugging, purse-snatching,
extortion, armed robbery)
- 25 (13) has been physically cruel to people
- B. If 18 or older, does not meet criteria for
Antisocial Personality Disorder.

30 Conduct disorder has been classified into three
diagnostic categories. The method of the present invention
is useful for the treatment of patients within any of these
diagnostic categories. The DSM-III-R diagnostic code and a
description of each of these subtypes are described in the
following paragraphs.

-11-

312.20 Group Type

5 The essential feature is the predominance of the conduct problems occurring mainly as a group activity with peers. Aggressive physical behavior may or may not be present.

312.00 Solitary Aggressive Type

10 The essential feature is the predominance of aggressive physical behavior, usually toward both adults and peers, initiated by the person (not as a group activity).

312.90 Undifferentiated Type

15 This is a subtype for children or adolescents with Conduct Disorder with a mixture of clinical features that cannot be classified as either Solitary Aggressive Type or Group Type.

20 Patients suffering from Conduct Disorder also commonly suffer concomitantly from Attention-deficit Hyperactivity Disorder, Bipolar Disorder, and Specific Developmental Disorders. The patient will benefit from the use of norepinephrine reuptake inhibitors in the amelioration of the symptoms of Conduct Disorder regardless of co-morbid conditions. Furthermore, a patient suffering
25 from Conduct Disorder and Attention-deficit Hyperactivity Disorder will receive benefit in the amelioration of symptoms of both conditions through the method of the present invention.

30 The method of the present invention is effective in the treatment of patients who are children, adolescents or adults, and there is no significant difference in the symptoms or the details of the manner of treatment among patients of different ages. In general terms, however, for purposes of the present invention, a child is considered to

-12-

be a patient below the age of puberty, an adolescent is considered to be a patient from the age of puberty up to about 18 years of age, and an adult is considered to be a patient of 18 years or older.

5

Inhibition of norepinephrine reuptake

The ability of compounds to inhibit the reuptake of norepinephrine may be measured by the general procedure of Wong, et al., *supra*.

10

Male Sprague-Dawley rats weighing 150-250 gm are decapitated and brains are immediately removed. Cerebral cortices are homogenized in 9 volumes of a medium containing 0.32 M sucrose and 10 mM glucose. Crude synaptosomal preparations are isolated after differential centrifugation at 1000 x g for 10 minutes and 17,000 x g for 28 minutes. The final pellets are suspended in the same medium and kept in ice until use within the same day.

15

Synaptosomal uptake of ³H-norepinephrine is determined as follows. Cortical synaptosomes (equivalent to 1 mg of protein) are incubated at 37°C for 5 minutes in 1 mL Krebs-bicarbonate medium containing also 10 mM glucose, 0.1 mM iproniazide, 1 mM ascorbic acid, 0.17 mM EDTA and 50 nM ³H-norepinephrine. The reaction mixture is immediately diluted with 2 mL of ice-chilled Krebs-bicarbonate buffer and filtered under vacuum with a cell harvester (Brandel, Gaithersburg, MD). Filters are rinsed twice with approximately 5 mL of ice-chilled 0.9% saline and the uptake of ³H-norepinephrine assessed by liquid scintillation counting. Accumulation of ³H-norepinephrine at 4°C is considered to be background and is subtracted from all measurements. The concentration of the test compound required to inhibit 50% of the ³H-norepinephrine accumulation (IC₅₀ values) are determined by linear regression analysis.

20

25

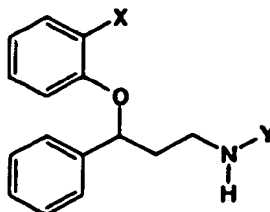
30

-13-

We claim:

1. A method of treating conduct disorder comprising administration to a patient in need of such treatment an effective amount of a norepinephrine reuptake inhibitor.

2. A method of Claim 1 wherein the norepinephrine reuptake inhibitor is selected from the group consisting of tomoxetine, reboxetine, duloxetine, venlafaxine, milnacipran, and a compound of formula I:



I

wherein X is C₁-C₄ alkylthio, and Y is C₁-C₄ alkyl or a pharmaceutically acceptable salt thereof.

3. A method of Claim 2 wherein the norepinephrine reuptake inhibitor is tomoxetine, reboxetine, or a compound of formula I.

4. A method of Claim 3 wherein the norepinephrine reuptake inhibitor is tomoxetine.

5. A method of Claim 3 wherein the norepinephrine reuptake inhibitor is reboxetine.

6. A method of Claim 3 wherein the norepinephrine reuptake inhibitor is (R)-N-methyl-3-(2-methylthiophenoxy)-3-phenylpropylamine.

7. A method of any of claims 1-6 wherein the group type of conduct disorder is treated.

8. A method of any of claims 1-6 wherein the solitary aggressive type of conduct disorder is treated.

9. A method of any of claims 1-6 wherein the undifferentiated type of conduct disorder is treated.

10. A method of claim 8, 9, or 10 wherein the norepinephrine reuptake inhibitor is tomoxetine hydrochloride.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/18103

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/135

US CL : 514/651

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/651

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE, DERWENT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,441,985 A1 (FOREMAN et al.) 15 August 1995, col. 8, lines 67-68.	1-9

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

29 SEPTEMBER 1998

Date of mailing of the international search report

24 DEC 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

ZORREN FAY

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/18103

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 10
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6A(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)